New developments in hepatitis A control

LILIAN YUAN, MD, FRCPC

SUMMARY

An inactivated vaccine for hepatitis A was recently licensed in Canada. This is the first important development in control of the disease in 50 years. This article presents new information about the vaccine and about the groups who might benefit from it. It also provides a review of the clinical and epidemiological aspects of hepatitis A.

RÉSUMÉ

Le Canada a récemment autorisé un vaccin inactivé contre l'hépatite A. Depuis 50 ans, il s'agit du premier développement majeur pour contrôler cette maladie. Cet article présente les nouveaux renseignements concernant ce vaccin et identifie les groupes qui peuvent en bénéficier. L'article présente également une revue des aspects cliniques et épidémiologiques de l'hépatite A.

Can Fam Physician 1995;41:1199-1205.

FOR CENTURIES, HEPATITIS A has caused epidemics of jaundice among civilian and military populations.[1] Understanding of the clinical and epidemiological features of the disease grew over time, but the virus was not identified until 1973.[2] Subsequent advances in techniques for propagating hepatitis A virus in cell culture[3] made the development of vaccines possible. The recent licensure of a hepatitis A vaccine in Canada calls for an examination of the role of vaccine in the prevention of disease. This article gives an overview of the clinical and epidemiological aspects of hepatitis A and discusses the potential uses of the vaccine.

To identify relevant articles, the English-language MEDLINE database was searched from 1980 to 1994 for the following key words in titles or abstracts: hepatitis A or infectious hepatitis or viral hepatitis, and epidemiology or prevention or control or outbreak or epidemic or vaccine. In addition, disease trends in Canada were compiled from data provided by Health Canada's Laboratory Centre for Disease Control (LCDC) and by Statistics Canada.

Dr Yuan *is an Assistant Professor in the Department of Preventive Medicine and Biostatistics at the University of Toronto.*

Hepatitis A virus

Hepatitis A is a small, nonenveloped, ribonucleic acid virus of the family Picornaviridae.[1] A single serotype is believed to exist worldwide.[2] Hepatitis A spreads readily because it can survive in a range of physical and chemical environments. It remains infectious indefinitely when frozen below -20°C; it is resistant to acid pH and to heating for several hours at 60°C; and it can withstand drying and storage at room temperature for months.[4,5] However, it can be destroyed by boiling for at least 1 minute and by disinfectants, such as chlorine.[4,5]

Clinical features

Clinical signs and symptoms of hepatitis A are highly dependent on age. Children younger than 2 years are often asymptomatic, and less than 10% of children younger than 6 years develop typical illness with jaundice. On the other hand, most adults develop symptoms of fever, malaise, nausea, diarrhea, and jaundice.[6]

Individuals with clinically apparent disease usually recover completely in 2 to 6 months,[6] but some develop fulminant hepatitis. Underlying liver disease, such as chronic hepatitis B infection, appears to predispose patients to more severe outcomes.[6] The case-fatality rate

is generally low, but increases with age (*Table 1*[7]). In Canada from 1988 to 1991, the overall case-fatality rate was 0.2%, but the rate for adults older than 60 years was 50 times higher than for children between 5 and 19 years old.[8]

Hepatitis A is most commonly transmitted by the fecal-oral route[7]; however, transmission through blood transfusions[9] and from non-human primates[10] have been documented. The mean incubation period is about 28 days (range 15 to 50 days),[5] and individuals are infectious during the late incubation period and the first week of illness.[11] This disease has no chronic carrier state, and a single infection is believed to result in lifelong immunity.[11]

Table 1. **Hepatitis A case-fatality rates in Canada, 1988 to 1991**

AGE GROUP (Y)	CASE-FATALITY RATE PER 1000
<5	0
5-19	0.6
20-39	0.8
40-59	6.7
>60	30.2
Overall	2.2

Compiled from data published by Statistics Canada.[7]

Diagnosis of acute hepatitis A requires detection of immunoglobulin M anti–hepatitis A virus (IgM anti-HAV). The IgM anti-HAV reaches peak levels during the acute or early convalescent phase and declines over 3 to 4 months.[6] On the other hand, immunoglobulin G anti–hepatitis A virus (IgG anti-HAV) reaches peak levels in the convalescent phase and remains for life.[6]

Epidemiology of hepatitis A

In Canada during the past decade, 1000 to 3000 cases have been reported annually for an incidence rate of 5 to 10 per 100 000 (*Figure 1*). Because of the presence of subclinical cases and the need for confirmatory testing by serology, underdiagnosis is likely. In developed countries, the true incidence of hepatitis A has been estimated at four to five times higher than currently reported.[12] An analysis of data collected during several decades shows that hepatitis A occurs in cyclic epidemics approximately every 10 years[13]; this feature was most prominent in the decades before the 1970s when incidence rates started to decline.

Incidence reported from different regions of Canada has varied from fewer than 1 per 100 000 in the Maritimes to more than 15 per 100 000 in some western provinces (personal communication from LCDC). The highest age-specific incidence rate and the greatest number of cases occur among adolescents and young adults (*Figure 2*). The ratio of male to female cases is 1.3:1,[13] but no evidence indicates that male patients are particularly susceptible to hepatitis A.[12]

Several risk factors have been associated with hepatitis A. In the United States, about 30% of cases report direct contact with another case, 10% to 15% are employed at or attend day-care centres, 11% report a history of injection drug use, 4% report recent international travel, and 3% are related to food- or water-borne outbreaks.[13] For 40% of cases, no risk factors are identified.[13]

Outbreaks

Hepatitis A outbreaks have been reported from a variety of settings: schools,[14] residential institutions,[15] correctional facilities,[16] day-care centres,[17,18] and hospitals.[19] In the United States, many outbreaks have occurred in large day-care centres, and those at greatest risk of infection appear to be people in contact with diapered toddlers.[17,18] Children are usually asymptomatic but act as transmitters of disease to adults.[18]

Outbreaks among men who have sex with men[20,21] and among injection drug users[22,23] have also been described. In 1991, homosexual communities in Canada (Toronto, Montreal), the United States (Denver,

San Francisco, New York),[20] and Australia (Sydney, Melbourne)[20] reported concurrent outbreaks of hepatitis A. Sexual practices perceived as "safe" (eg, oral-anal contact) and the mobility of individuals in the homosexual community likely enhanced the spread of infection from city to city and country to country.

Community-wide outbreaks[24] in close-knit religious[25] and aboriginal[26] groups have also been reported. These outbreaks can be prolonged and difficult to control.[25] An outbreak lasted 20 months in five Inuit communities on Baffin Island during 1991 and 1992. Nearly 500 cases were reported: 94% were children younger than 20 years. Nine children required hospitalization and three died of hepatorenal failure (personal communication from Dr R. Allen, Government of the Northwest Territories).

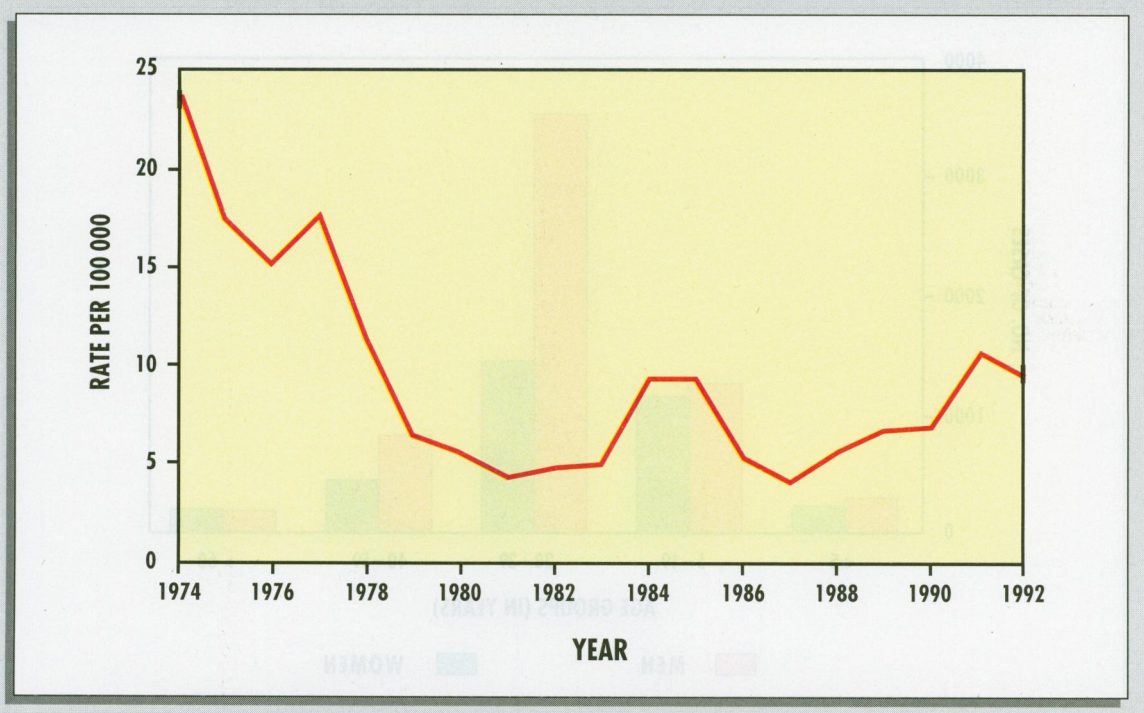
Hepatitis A–contaminated food[27,28] and water[29] have also resulted in several outbreaks, but they account for only a small proportion of reported cases in developed countries.[30] One of the largest known outbreaks in history occurred in 1988 in Shanghai, China, when more than 300 000 people developed hepatitis A after eating contaminated clams.[28]

Prevention and control

The most important measures for preventing fecal-oral spread are good personal hygiene, adequate food handling practices, clean drinking water, and proper sanitary facilities. Additional control measures include passive immunization with immune globulin and active immunization with hepatitis A vaccine.

Immune globulin. Human serum immune globulin has been known for more than 50 years to protect (perhaps by preventing infection[2] or perhaps by attenuating symptoms of hepatitis A in infected persons[2]) against hepatitis A.[31] Several studies[31,32] have demonstrated its effectiveness in pre-exposure and postexposure prophylaxis. However,

Figure 1. **Hepatitis A incidence rates for Canada, 1974 to 1992**



Compiled from data supplied by the Laboratory Centre for Disease Control, Health Canada.

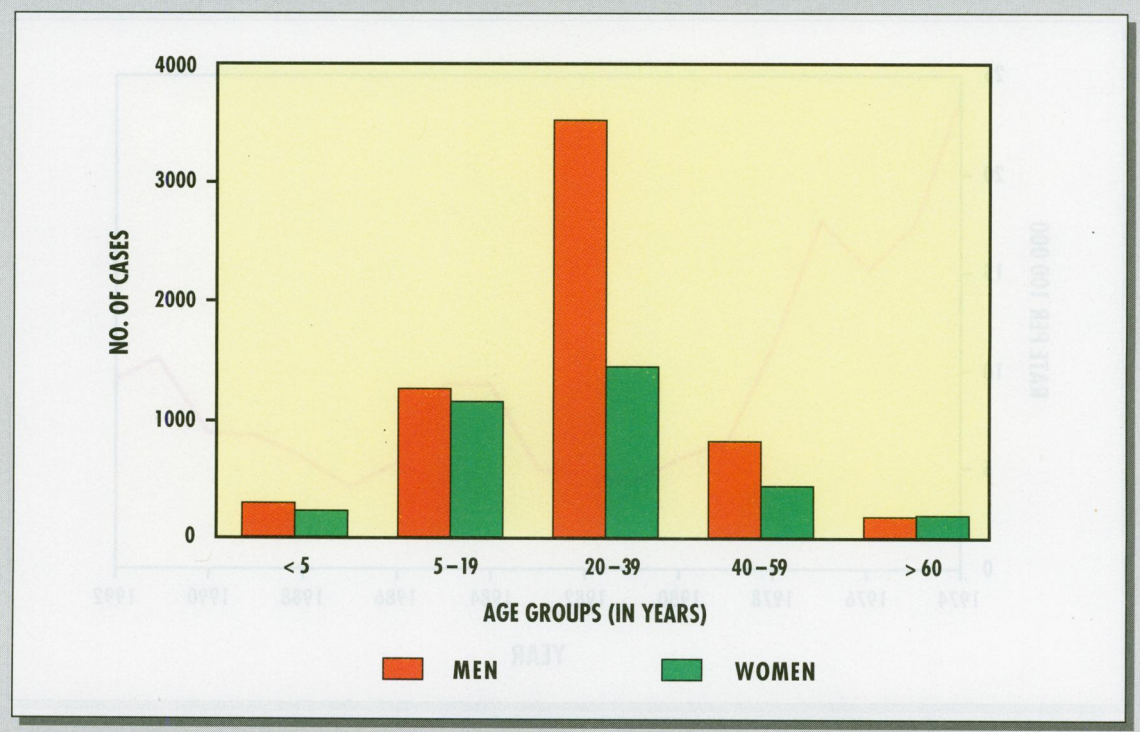
protection tends to be short-lived, and injections must be repeated every 3 to 6 months to maintain immunity.[33,34]

For pre-exposure prophylaxis, such as for travel to countries where hepatitis A is endemic, a single intramuscular dose of immune globulin of 0.02 mL/kg body weight will provide 3 months of protection. For 4 to 6 months of protection, the dose must be increased to 0.06 mL/kg body weight.[33,34] For postexposure prophylaxis for household and sexual contacts of infected persons, a dose of 0.02 mL/kg body weight should be given as soon as possible after exposure.[33,34] Efficacy of 80% to 90% has been shown only when the vaccine was administered within 2 weeks of exposure.[35]

Hepatitis A vaccines. Both inactivated and live attenuated hepatitis A vaccines are currently being studied,[36] but most progress is being made with two inactivated vaccines. One is a formalin-inactivated vaccine produced from hepatitis A strain CR326.[36] Most studies of this vaccine have used a two-dose schedule where vaccine is administered at 0 and 6 months.[37] Werzberger et al[38] reported seroconversion in 99% of vaccinated children aged 2 to 16 years after immunization with a single dose, and no cases of hepatitis A from 3 weeks to 6 months afterward. This vaccine is currently unlicensed.

The other inactivated vaccine was recently licensed in Canada. This is a whole-virion vaccine containing hepatitis A strain HM175, inactivated by formalin, and adsorbed onto alum.[39,40] The vaccination schedule is two primary doses 1 month apart and a booster dose 2 to 12 months later.[41] Results from clinical trials show that 1 month after the first dose, approximately 96% of those vaccinated seroconvert; 1 month after the second dose, 99.8% have seroconverted; and after the booster dose, 100%.[41] A protective efficacy of 97% was demonstrated in a large randomized,

Figure 2. **Age and sex distribution of hepatitis A cases in Canada, 1988 to 1992**



Compiled from data supplied by the Laboratory Centre for Disease Control, Health Canada.

controlled field trial in Thailand with 40 000 schoolchildren.[42] More than 55 000 people have tolerated the vaccine well to date. Mild local pain lasting a day was the most common complaint (reported by about 40% of those vaccinated), and about 10% reported fatigue or headache.[41]

Studies have shown that simultaneous administration of immune globulin with hepatitis A vaccine results in an adequate, but slightly lowered, antibody response.[43,44] Therefore, the vaccine can be administered simultaneously with immune globulin when both rapid and long-term protection is desired, for example, for travelers who are leaving the country imminently. Also, hepatitis A and hepatitis B vaccines can be administered simultaneously at separate sites without concern about the immune response to either vaccine.[45]

We do not know how long immunity lasts after vaccination. Studies to date show that antibodies are sustained for at least 3 years after vaccination,[46] and mathematical modeling of the decay of vaccine-induced antibody has predicted that protective levels will last at least 10 years.[47]

Who should receive the hepatitis A vaccine? The vaccine has been suggested for travelers to countries where hepatitis A is endemic[39,45] and where the incidence of disease for individuals staying in above-average accommodations has been documented as 3 to 6 per 1000 per month of stay.[48] Military personnel or relief workers, who might be deployed to such countries, should also be considered for vaccination.[49] Other groups include laboratory workers who handle hepatitis A specimens,[49] handlers of non-human primates, staff and residents at day-care centres, staff at centres for the developmentally challenged,[49] sewage workers,[50] and food handlers.[30] Other groups who might be at higher risk of hepatitis A infection, such as injection drug users,[22,23] men who have sex with men,[21] and residents in isolated communities with poor sanitation,[26,27] might also benefit from vaccination.

Conclusion

Hepatitis A infection can result in a variety of symptoms ranging from subclinical disease to fulminant hepatitis and death. Age is the most important determinant of clinical presentation and disease severity. In developed countries, person-to-person spread by the fecal-oral route appears to be the most common mode of transmission. Control measures to date have emphasized personal hygiene, clean drinking water, proper sanitation, and the use of immune globulin. When active and long-term protection against the disease is required, hepatitis A vaccine can now be used. ■

Correspondence to: *Dr L. Yuan, Assistant Professor, Department of Preventive Medicine and Biostatistics, University of Toronto, 4th floor, McMurrich Building, Toronto, ON M5S 1A8*

References

1. Feinstone SM, Kapikian AZ, Purcell RH. Hepatitis A: detection by immune electron microscopy of a virus-like antigen associated with acute illness. *Science* 1973;182:1026-8.
2. Lemon SM. Type A viral hepatitis – new developments in an old disease. *N Engl J Med* 1985;313:1059-67.
3. Provost PJ, Hilleman MR. Propagation of human hepatitis A virus in cell culture in vitro. *Proc Soc Exp Biol Med* 1979;160:213-21.
4. Siegl G, Weitz M, Kronauer G. Stability of hepatitis A virus. *Intervirology* 1984; 22:218-26.
5. Provost PJ, Wolanski BS, Miller WJ, Ittensohn OL, McAleer WJ, Hilleman MR. Physical, chemical and morphologic dimensions of human hepatitis virus strain CR236. *Proc Soc Exp Biol Med* 1975;148:532-9.
6. Koff RS. Clinical manifestations and diagnosis of hepatitis A virus infection. *Vaccine* 1992; 10(Suppl 1):S15-7.
7. Statistics Canada. *Causes of death.* Catalogues 82-0035 and 84-208. Ottawa: Statistics Canada, 1990-1993.
8. Krugman S, Ward R, Giles JP. The natural history of infectious hepatitis. *Am J Med* 1962;32:717-28.

Continued on page 1204

9. Hollinger FB, Narayan CK, Oefinger PE, Yawan DH, Schmulen AC, Dreesman GR, et al. Posttransfusion hepatitis type A. *JAMA* 1983;250:2313-7.
10. Dienstag JL, Davenport FM, McCollum RW, Hennessey AV, Klatskin G, Purcell RH. Nonhuman primate-associated viral hepatitis type: serologic evidence of hepatitis A viral infection. *JAMA* 1976;236:462-4.
11. Hadler SC. Global impact of hepatitis A virus infection. In: Hollinger FB, Lemon SM, Margolis HS, editors. *Viral hepatitis and liver disease: proceedings of the 1990 International Symposium on Viral Hepatitis and Liver Disease.* Baltimore: Williams and Wilkins, 1991.
12. Gust ID. Epidemiological patterns of hepatitis A in different parts of the world. *Vaccine* 1992;10(Suppl 1):S56-8.
13. Shapiro CN, Coleman PJ, McQuillan GM, Alter MJ, Margolis HS. Epidemiology of hepatitis A: seroepidemiology and risk groups in the USA. *Vaccine* 1992;10:S59-62.
14. Reid RJ, Carter JM. Hepatitis A investigation and control of outbreaks in two primary schools. *Public Health* 1986;100:69-75.
15. Tassopoulous NC, Roumeliotou-Karayannis A, Sakka M, Ticehurst J, Mihalik K, Stephanou T, et al. An epidemic of hepatitis A in an institution for young children. *Am J Epidemiol* 1987; 125:302-7.
16. Holter E, Siebke J-C. Hepatitis A in young Norwiegan drug addicts and prison inmates. *Infection* 1988;16:91-4.
17. Shapiro CN, Hadler SC. Hepatitis A and hepatitis B virus infections in day-care settings. *Pediatr Ann* 1991;20:435-41.
18. Hadler SC, McFarland L. Hepatitis in daycare centers: epidemiology and prevention. *Rev Infect Dis* 1986;8:548-57.
19. Doebbeling BN, Li N, Wenzel RP. An outbreak of hepatitis A among health care workers: risk factors for transmission. *Am J Public Health* 1993;83:1679-84.
20. Hepatitis A among homosexual men – United States, Canada and Australia. *MMWR Morb Mortal Wkly Rep* 1992;41:155-64.
21. Coutinho RA, Albrecht-Van Lent P, Lelie N, Nagelkerke N, Kuipers H, Rijsdijk T. Prevalence and incidence of hepatitis A among male homosexuals. *BMJ* 1983; 287:1743-5.
22. Jin A, Bardsley J. Intravenous drug use and hepatitis A: an investigation of an outbreak. *Can J Public Health* 1990;81:79-81.
23. Jenkerson SA, Middaugh JP, Pittman SL, Redeker AG, Roberto RR, Hadler JL, et al. Hepatitis A among drug abusers. *MMWR Morb Mortal Wkly Rep* 1988;37:297-305.
24. Shaw RE, Sudman JH, Smith SM, Williams DL, Kapell LA, Hadler SC, et al. A community-wide epidemic of hepatitis A in Ohio. *Am J Epidemiol* 1986;123:1057-65.
25. Pavia AT, Nielsen L, Arminton L, Thurman DJ, Tierney E, Nichols CR, et al. A community-wide outbreak of hepatitis A in a religious community: impact of mass administration of immune globulin. *Am J Epidemiol* 1990;131:1085-93.
26. Bulkow LR, Wainwright RB, McMahon BJ, Middaugh JP, Jenkerson SA, Margolis HS, et al. Secular trends in hepatitis A virus infection among Alaska natives. *J Infect Dis* 1993; 168:1017-20.
27. Niu MT, Polish LB, Robertson BH, Khanna BK, Woodruff BA, Shapiro CN, et al. Multistate outbreak of hepatitis A associated with frozen strawberries. *J Infect Dis* 1992;166:518-24.
28. Xu ZY, Li ZH, Wang JX, Xiao ZP, Dong DX. Ecology and prevention of shellfish-associated hepatitis A epidemic in Shanghai, China. *Vaccine* 1992; 10(Suppl 1):S67-8.
29. Bloch AB, Stramer SL, Smith D, Margolis HS, Fields HA, McKinley TW, et al. Recovery of hepatitis A virus from a water supply responsible for a common source outbreak of hepatitis A. *Am J Public Health* 1990;80:428-30.
30. World Health Organization. Prevention of foodborne hepatitis A. *Wkly Epidemiol Rec* 1993;68:25-32.
31. Stokes J, Neefe J. The prevention and attenuation of infectious hepatitis by gamma globulin. *JAMA* 1945;127:144-5.
32. Navens WP, Paul JR. Prevention of infectious hepatitis with gamma globulin. *JAMA* 1945;129:270-2.
33. National Advisory Committee on Immunization. *Canadian immunization guide.* 4th ed. Ottawa: Health and Welfare Canada, 1994.
34. Immunization Practices Advisory Committee. Protection against viral hepatitis. *MMWR Morb Mortal Wkly Rep* 1990; 39(Suppl 2):1-26.
35. Mosley JW, Reisler DM, Brachott D, Roth D, Weiser J. Comparison of two lots of

immune serum globulin for prophylaxis of infectious hepatitis. *Am J Epidemiol* 1968;87:539-50.
36. Deinhardt F. Prevention of viral hepatitis A: past, present and future. *Vaccine* 1992;10:S10-3.
37. Shouval D, Ashur Y, Adler R, Lewis JA, Armstrong ME, Davides JP, et al. Single and booster dose response to an inactivated hepatitis A vaccine: comparison with immune serum globulin prophylaxis. *Vaccine* 1993;11:S9-S14.
38. Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *N Engl J Med* 1992;327:453-7.
39. Hepatitis A: a vaccine at last. *Lancet* 1992;339:1198-9.
40. Scheifele DW, Bjornson GJ. Evaluation of inactivated hepatitis A vaccine in Canadians 40 years of age or more. *Can Med Assoc J* 1993;148:551-5.
41. National Advisory Committee on Immunization. Statement on the prevention of hepatitis A infection. *Can Commun Dis Rep* 1994;20:133-43.
42. Innis BL, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Suntayakorn S, et al. Field efficacy trial of inactivated hepatitis A vaccine among children in Thailand [abstract]. *Vaccine* 1992;10:S159.
43. Green MS, Cohen D, Lerman Y, Sjorgren M, Binn LN, Zur S, et al. Depression of the immune response to an inactivated hepatitis A vaccine administered concomitantly with immune globulin. *J Infect Dis* 1993;168:740-2.
44. Leentvaar-Kuijpers A, Coutinho RA, Brulein V, Safary A. Simultaneous passive and active immunization against hepatitis A. *Vaccine* 1992;10:S138-41.
45. Ambrosch F, Andre F, Delem A, D'Hondt E, Jonas S, Kunz C, et al. Simultaneous vaccination against hepatitis A and B: results of a controlled study. *Vaccine* 1992;10:S142-5.
46. Berger R, Just M. Vaccination against hepatitis A: control 3 years after the first vaccination. *Vaccine* 1992;10:295.
47. Wiedermann G, Ambrosch F, Andre FE, D'Hondt E, Delem A, Safary A, et al. Persistence of vaccine-induced antibody to hepatitis A virus. *Vaccine* 1992;10(Suppl 1):S129-31.
48. Steffen R. Hepatitis A and hepatitis B: risks compared with other vaccine preventable diseases and immunization recommendations. *Vaccine* 1993;11:518-20.
49. Jilg W. Adult use of hepatitis A vaccine in developed countries. *Vaccine* 1993;11(Suppl 1):S6-8.
50. Poole CJM, Shakespeare AT. Should sewage workers and carers for people with learning disabilities be vaccinated for hepatitis A? *BMJ* 1993;306:1102.

• • •